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The Impact of Circadian Rhythms on the Development of Depression

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Abstract. Human beings exist in a 24-hour cycle where day and night alternate in a daily pattern. Circadian rhythms, which connects the body and environment successfully, have developed in nearly all living organisms. The suprachiasmatic nucleus (SCN), a circadian timer situated in the hypothalamus, aligns our internal biological clocks with the Earth's 24-hour day-night cycle. This synchronization is achieved through a pathway from the retina. These rhythms regulate a wide array of physiological processes, such as hunger, sleep patterns, physical activity, hormone. It is noteworthy that mood also exhibits a daily pattern, and disturbances in the circadian system are associated with mood-related issues. People with depression frequently exhibit irregularities in their sleep, appetite, activity levels, and cortisol release, indicating that the stability of circadian rhythms is a key contributor to the onset and physiological processes of depressive disorders. This article reviews recent research findings in both humans and animal models that connect disrupted circadian rhythms with depressive disorders. Understanding this link could lead to innovative therapeutic approaches, such as treatments aimed at restoring circadian rhythm integrity, and may also open doors for preventive measures targeting those at risk of mood disorders. Continued research in this area holds promise for improving mental health outcomes by addressing the underlying biological mechanisms tied to circadian rhythms and mood regulation.

Keywords: circadian rhythm, depression, mood disorder.

1. Introduction

Circadian rhythms, which are innate 24-hour cycles governing a broad spectrum of physiological and behavioral processes, are a fundamental aspect of life across various phyla [1]. These rhythms are not only mirrored to the Earth's Day-night cycle but also aligned with an organism's internal clock, the suprachiasmatic nucleus (SCN) in mammals [2]. The SCN coordinates external signals like light exposure and temperature with internal processes to maintain homeostasis [3]. Disruptions to these rhythms, often due to modern lifestyle factors like shift work, jet lag, and excessive artificial light, are linked to various health problems, including mood disorders [4].

Depression, a complex mental health condition, is increasingly being recognized as having a significant circadian component. The daily mood variations experienced by individuals with depression, such as early morning awakening, afternoon slump, and evening worsening of symptoms, are telltale signs of circadian dysregulation [5].

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The molecular underpinnings of circadian rhythms involve a transcriptional-translational feedback loop, with key components like CLOCK, BMAL1, PER, and CRY proteins [6]. Dysregulation of this loop, possibly due to genetic mutations or environmental stressors, can lead to mood disorders [7]. For example, variations in genes that govern circadian rhythms, such as CLOCK and ARNTL, have been correlated with mood disorders like depression and bipolar disorder [8]. Moreover, the SCN's sensitivity to light is compromised in depressed individuals, suggesting a weakened entrainment mechanism [5].

Stress, a known trigger for depression, also impacts circadian rhythms. Chronic stress can lead to a phase shift in the expression of PER2, a key circadian protein, disrupting the normal sleep-wake cycle and contributing to depressive symptoms [9]. Furthermore, the serotonergic system, which is closely linked to mood regulation, exhibits a circadian pattern, and its disruption can lead to depression [5]. Serotonin reuptake inhibitors, commonly used antidepressants, can also affect circadian rhythms, highlighting the interconnected nature of these systems [10].

Therapies that focus on the body's daily rhythm, such as light therapy and chronotherapy, have shown promise in treating depression [11]. Light therapy, in particular, has been effective in seasonal affective disorder, a subtype of depression closely tied to circadian dysfunction [12]. Additionally, drugs like agomelatine, which has melatonin agonist properties, have demonstrated antidepressant effects by resetting the circadian clock [13].

The circadian system plays a pivotal role in the development and treatment of depression. This review seeks to delve deeper into the complex interplay between circadian rhythms and the development of depression, investigating the underlying mechanisms, implications, and potential therapeutic strategies.

2. Disruptions of the Circadian System

2.1. The SCN and Its Role in Circadian Regulation

The central pacemaker in mammals, including humans, is known as the SCN, which is a pair of structures situated within the hypothalamus. Each nucleus has a volume of approximately 0.25 cubic millimeters [14]. In the SCN of mammals, a molecular oscillator maintains the regular rhythm of the circadian cycle, and is thought to be responsible for the rapid, innate rhythms observed in mammals' communication signals [15, 16].

2.2. Environmental and Non-Photic Inputs to the SCN

Effective interaction with the environment isn't solely dependent on a central clock; it also necessitates sensory pathways that convey environmental and bodily information to the SCN for proper entrainment. Additionally, it requires output pathways to disseminate temporal cues to the body, ensuring that physiological processes are synchronized with the circadian cycle [17].

For all timekeeping mechanisms to align with the Earth's rotation and the solar cycle, they must be synchronized both internally and with external cues [18]. The primary external cue for this synchronization is light. Ambient light influences the SCN, and the retina also sends light-sensitive signals to the SCN through the retinohypothalamic tract (RHT) [19, 20].

Beyond the external light, the SCN is also responsive to non-light-related cues that originate internally [21, 14]. Key pathways for this include the geniculohypothalamic tract (GHT), which conveys both non-light-related and light-related information (via the intergeniculate leaflet; IGL), as well as the raphe-hypothalamic tract (raphe-HT) [22, 23]. Furthermore, the SCN activity is regulated by non-light cues through neurotransmitters and hormones, like serotonin and melatonin, in addition to oscillators in other bodily tissues [24, 25].

2.3. Consequences of Circadian Disruptions on Health

Within the realms of human chronobiology and sleep research, substantial efforts have focused on two prominent impacts of light: (1) the immediate inhibition of melatonin synthesis upon light exposure, and (2) the capacity of light to alter the circadian rhythm. However, these impacts do not stem from a single

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pathway, and there is no straightforward correlation between the suppression of melatonin and the shifting of circadian phases. Emerging evidence suggests that these two responses may actually be distinct processes [25]. Therefore, it is inappropriate to use one as a substitute for the other when considering their physiological impacts [25].

In addition to light, the typical day-night cycle can be disrupted by factors such as nighttime artificial lighting, shift work, reduced sleep duration or quality, and transmeridian travel, which can cause jet lag [26]. Furthermore, aging, dementia, and neurodegenerative conditions like Parkinson's and Huntington's diseases can lead to a decline in the effectiveness of circadian rhythms [27]. Considering the 24-hour cyclical nature of many physiological processes, it is not surprising that disruptions to circadian rhythms are associated with a variety of health problems, and these include metabolic issues, cancers, and psychological conditions such as cognitive deterioration, as well as depression, which is of particular relevance to this review [28].

3. Circadian Rhythm Disruptions and Mood Disorders

Research has demonstrated that mood fluctuations are affected by an intricate and non-linear interplay between a person's circadian circle and their duration of wakefulness. Notably, even slight shifts in the timing of the day-night cycle can lead to significant mood changes [25].

Light exerts its influence on mood through multiple mechanisms: it can directly alter the levels of neurotransmitters like serotonin, which is crucial for mood control, and it can also synchronize and stabilize circadian rhythms. This helps to correct circadian misalignment and sleep disturbances, which are prevalent in individuals with mental health conditions. Consequently, over the past few decades, light therapy has become increasingly popular for managing mood disorders and other psychiatric conditions [29].

Apart from the SCN's role in regulating circadian light effects, recent research has uncovered a retinal pathway to the habenula that contributes to the mood-altering effects of light in animal studies [30].

3.1. Depressive Disorder and Circadian Disruptions

Major depressive disorder (MDD) is distinguished by mood changes, most commonly manifested as heightened feelings of sadness or irritability, along with at least one additional psychophysiological symptom such as disturbances in sleep, changes in libido or appetite, anhedonia (inability to feel pleasure), psychomotor slowing (reduced speech or movement), crying spells, or thoughts of suicide [31]. For a diagnosis of MDD, these symptoms are required to last for at least two weeks and significantly disrupt regular daily activities [31]. MDD is a common illness worldwide. Based on the Global Burden of Disease Consortium's research, which analyzed the occurrence and prevalence of 328 diseases across 195 countries globally from 1990 to 2016, MDD was among the top ten disease-related burdens in almost every country surveyed [32]. The global prevalence of MDD is on the rise. Between 2005 and 2018, diagnoses of depression among US adults increased, with the prevalence rate growing from 6.8% to 7.1% [33]. Interestingly, the prevalence of MDD is linked to the degree of societal modernization, which might be attributed to the heightened circadian disruptions characteristic of modern life (including night-time artificial lighting, shift work, and time zone changes) or to the combined effects of circadian disruptions and other environmental elements present in more industrialized nations [34, 35].

While there is a scarcity of human studies that directly explore the connection between disrupted circadian rhythms and MDD, with the majority focusing on depression in general, some investigations have looked into the relationship between shift work—a known disruptor of circadian rhythms—and MDD, yielding inconsistent findings [36]. A study involving approximately 4,000 South Koreans found a significantly higher prevalence of MDD among shift and night workers compared to day workers [37]. In contrast, a French study did not find a link between shift work and MDD [35, 38]. However, when considering all types of depression, a clearer pattern emerges, with shift work being strongly linked to an increased risk [35]. A meta-analysis indicated that nighttime shift employees have a 40% greater chance of developing depression than day workers [39]. This suggests that while the specific link

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between circadian disruption and MDD may be less studied, the overall effect of disrupted circadian rhythms, as experienced by shift workers, is more consistently associated with depressive disorders.

3.2. Mechanisms of how Circadian Rhythm affecting mood

3.2.1. Circadian Cycles and Sleep-Wake Cycle. Circadian rhythms, which are approximately 24-hour cycles, are crucial for the sleep-wake pattern. These rhythms are governed by the SCN in the hypothalamus and are aligned with external light-dark cycles. Disturbances to the body's internal clock can result in sleep disturbances and subsequently affect mood [4].

Disturbances in circadian rhythms can stem from various exogenous factors like artificial lighting or endogenous factors like genetic predispositions, leading to sleep issues such as nonrestorative sleep, excessive sleepiness, and challenges with falling asleep or remaining asleep [40]. The two primary endogenous sleep-wake disturbances are delayed sleep-wake phase syndrome and advanced sleep-wake phase syndrome. The former causes difficulty in falling asleep at conventional times, leading to late wake times, while the latter results in premature sleep and early morning awakenings. Both conditions disrupt a person's capacity to keep a consistent sleep pattern, exacerbating symptoms of depression.

In addition to these endogenous disorders, external circadian rhythm disruptions like shift work disorder and jet lag, occur when the body's internal clock becomes desynchronized with external schedules, such as irregular work hours or rapid travel across time zones. These disruptions can trigger or worsen depressive symptoms by altering sleep patterns and affecting the body's natural mood regulation processes [7]. Studies have shown that sleep-wake cycle disturbances, particularly those resulting from circadian rhythm disruptions, are closely associated with mood regulation. For example, poor sleep quality, shortened sleep duration, and irregular sleep patterns can raise the likelihood of mood disorders, including depression. The connection between sleep and mood highlights the significance of maintaining a stable circadian rhythm to support mental health and emotional well-being.

3.2.2. Role of Light in Mood Regulation. Light, a potent synchronizer of the circadian rhythm, is essential for regulating human mood. Light affects mood by influencing circadian rhythms, sleep patterns, and directly interacting with brain areas linked to emotional regulation [39]. Behavioral patterns of light exposure, such as spending time outdoors during the day and controlling indoor light before bedtime, have been found to predict mood. Morning light exposure tends to shift the circadian rhythm earlier, while evening light exposure can cause a delay in the rhythm [38]. Blue-enriched light, in particular, has been shown to have a significant impact on alertness and mood. Morning exposure to this type of light can boost a positive mood, while afternoon exposure may increase negative mood.

Understanding the role of light in mood regulation is crucial for devising approaches to improve mental health and well-being. Encouraging behaviors that promote healthy light exposure, such as spending time outdoors during the day and minimizing evening use of electronic devices, can have significant benefits for mood and overall health.

3.2.3. Retinal Pathway to the Habenula. The habenula, a crucial structure involved in stress response, reward processing, and circadian regulation, is linked directly to the eye through the retinal-habenula pathway. Unlike the SCN, this pathway bypasses the primary visual cortex, enabling it to influence mood independently of traditional circadian regulation. The retinal-habenula pathway influences various physiological functions, including the modulation of the hypothalamic-pituitary-adrenal (HPA) axis and melatonin production, and this pathway plays a role in managing mood. Stimulating this pathway with light has demonstrated antidepressant properties in animal models, suggesting a potential novel therapeutic target for mood disorders. In depression, disturbances in the HPA axis and melatonin dysregulation are common, leading to heightened stress responses and altered sleep patterns—two key contributors to depressive symptoms. The retinal-habenula pathway's ability to modulate these processes suggests that it may play a pivotal role in the onset and progression of depression Understanding the retinal pathway to the habenula could lead to novel treatments for mood disorders.

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Deep brain stimulation of the habenula is being explored as a potential treatment for treatment-resistant depression, with preliminary results showing remission in patients.

4. Treatment of circadian disruptions in depression

Approximately 80% of individuals with depression experience disruptions in their sleep patterns, as noted by Armitage in 2007. Melatonin has emerged as a promising treatment option for depression, particularly for individuals whose depressive symptoms are linked to circadian rhythm disruptions. Melatonin helps regulate the sleep-wake cycle and is crucial for maintaining a stable circadian rhythm. In depression, where sleep patterns are often disturbed, melatonin supplementation has shown benefits by improving sleep quality and reducing mood symptoms. Studies in animal models, such as those involving corticosterone-induced depression, have demonstrated that melatonin can alleviate depressive behaviors, suggesting that regulating melatonin levels may be a key mechanism for managing depression [1]. These properties of melatonin, combined with its ability to stabilize circadian rhythms, make it a valuable adjunctive therapy in treating mood disorders. Therefore, administering melatonin, particularly in rhythmically controlled doses, could provide relief for patients experiencing circadian rhythm disruptions as part of their depressive symptomatology.

Additionally, it is known that various non-pharmacological interventions for depression aim at the restoration of circadian rhythms, including bright light therapy, phase advance and sleep deprivation therapy [1]. Bright light therapy is recognized as an efficient, non-invasive, and well-accepted treatment, especially for individuals suffering from Seasonal Affective Disorder (SAD). The practice of sleep deprivation, typically involving a full night without sleep, has demonstrated efficacy in approximately 50%-60% of individuals with depression. Sleep phase advance therapy involves instructing individuals with depression to alter their sleep schedule by waking up and going to bed earlier, with the goal of realigning their circadian rhythm [40].

5. Conclusions

The circadian system plays a pivotal role in modulating mood-related behaviors. This system is regulated internally but is significantly affected by external factors, especially unnatural light exposure and stress, which can disrupt circadian rhythms and potentially trigger depression. Disturbances in circadian cycles may result in mental disorders and depression. In cases of circadian disruptions associated with depression, melatonin has positive effects. Additionally, numerous non-drug treatments for depression play a significant role in alleviating depressive symptoms.

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